IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LIMITED Defendants.	Civil Action No. 04-171-KAJ **REDACTED VERSION** **August 4, 2006**

PLAINTIFF GLAXO GROUP LIMITED'S ANSWERING BRIEF TO DEFENDANT TEVA'S OPENING BRIEF IN SUPPORT OF ITS CLAIM CONSTRUCTION

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MISCELLANEOUS.

I. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiff Glaxo Group Limited ("Glaxo") provided a statement concerning the nature and stage of the proceedings in its "Opening Claim Construction Brief Construing the Disputed Claim Terms of Glaxo's U.S. Patent No. 5,068,249" submitted on June 30, 2006 (D.I. 97) ("Glaxo's Opening Claim Construction Brief"), to which this Court is respectfully referred.

Pursuant to Paragraph 12 of the Scheduling Order, Glaxo submits this answering brief in response to "Teva's Opening Brief in Support of Its Claim Construction" submitted on June 30, 2006 (D.I. 101). In support of its answering brief, Glaxo relies on the Declarations of Oren D. Langer[1] and Bradley D. Anderson, Ph.D.[2] For the reasons discussed herein, Glaxo respectfully requests that the Court adopt Glaxo's claim construction for the disputed and undisputed claim elements.

II. SUMMARY OF ARGUMENT

The claim construction proposed by Glaxo is (1) consistent with the intrinsic evidence of Glaxo's U.S. Patent No. 5,068,249 ("the '249 patent"), (2) in accordance with Federal Circuit law, and (3) consistent with the plain and ordinary meaning of the claim language to one of ordinary skill in the art of pharmaceutical formulation and development. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). The claim construction proposed by

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[1] "Langer Decl." refers to the "Declaration of Oren D. Langer, Esq., in Support of Plaintiff Glaxo Group Limited's Opening Claim Construction Brief and Summary Judgment Motions on U.S. Patent No. 5,068,249" submitted on June 30, 2006. (D.I. 99 (Exhibits 1-25) and D.I. 100 (Exhibits 26-48)). "Langer Suppl. Decl." refers to the "Supplemental Declaration of Oren D. Langer, Esq., in Support of Plaintiff Glaxo Group Limited's Answering Brief to Teva's Motion for Summary Judgment of Non-Infringement" submitted herewith.

[2] "Anderson Decl." refers to "Declaration of Bradley D. Anderson, Ph.D., in Support of Plaintiff Glaxo Group Limited's Opening Claim Construction Brief on U.S. Patent No. 5,068,249" submitted on June 30, 2006. (D.I. 98).

Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Limited ("Teva" or "defendant") is not consistent or in accordance with any of these. In particular:

- Defendant's proposed construction for "ethanol" is incomplete, redundant, and undermines the purpose of claim construction, which is to provide meaning and to " 'elaborate the normally terse claim language in order to understand and explain, but not to change, the scope of the claims.' " *Embrex, Inc. v. Serv. Engr. Corp.*, 216 F.3d 1343, 1347 (Fed. Cir. 2000) (quoting *Scripps Clinic v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991)).

- Defendant's proposed construction of "a stabilizing effective amount of" improperly reads into the claims extraneous detailed measurement criteria from the prosecution history of the '249 patent. *See Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1348 (Fed. Cir. 2002) ("While a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history.").

- Defendant's proposed construction for "2.5% to 10% weight/volume ethanol" and "7% to 8% weight/volume ethanol" fails to recognize claim dependency and to apply Federal Circuit law concerning consistency of claim interpretation. *See* 35 U.S.C. § 112 (stating that dependent claims incorporate all of the limitations of the independent claim from which they depend); *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1356 (Fed. Cir. 2004) ("[S]ubject matter surrendered via claim amendments during prosecution is also relinquished for other claims containing the same limitation. This court follows this rule to ensure consistent

interpretation of the same claim terms in the same patent.") (citing *Builders Concrete, Inc. v. Bremerton Concrete Prods. Co.*, 757 F.2d 255, 260 (Fed. Cir. 1985)).

- Finally, defendant does not dispute Glaxo's construction of "aqueous formulation for oral administration" and "aqueous formulation of ranitidine suitable for oral administration." Glaxo respectfully requests that these claim elements be construed because they provide life and meaning to the claims of the '249 patent and are necessary in order to put the disputed claim elements into proper context. *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) ("If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim.") (quoting *Kropa v. Robie*, 187 F.2d 150, 152 (C.C.P.A. 1951)).

For these and the reasons set forth further below, Glaxo respectfully requests that the Court adopt Glaxo's proposed claim construction for the above-identified claim elements.

III. STATEMENT OF FACTS

A complete description and analysis of the technical background of the invention and of the specification, claims, and prosecution history of the '249 patent is contained in Glaxo's Opening Claim Construction Brief (D.I. 97), to which this Court is respectfully referred.

IV. ARGUMENT

A. Claim Construction Principles

Claim construction is a matter of law for the court to decide. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*). The Federal Circuit has stated that the objective of claim construction is to give claim terms " 'their ordinary and customary meaning,' " which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1312-13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation. . . . Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313.

To ascertain the ordinary and customary meaning of a claim term, "the court looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.' Those sources include 'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.' " *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id.* Additionally, "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.' " *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). Ultimately, "[t]he construction that stays true to the claim language and most naturally

aligns with the patent's description of the invention will be, in the end, the correct construction." *Id.* at 1316 (citing *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

In construing claim terms, the patent's prosecution history should be consulted so that the court can exclude any interpretation that was disclaimed during prosecution. *See id.* at 1317. "Disclaimers based on disavowing actions or statements during prosecution, however, must be both clear and unmistakable." *Sorensen v. ITC*, 427 F.3d 1375, 1378-79 (Fed. Cir. 2005). "Moreover, 'it is the applicant, not the examiner, who must give up or disclaim subject matter that would otherwise fall within the scope of the claims.' " *Id.* at 1379 (quoting *Innova*, 381 F.3d at 1124).

B. Construction Of Terms

1. Claims 1-12: "ethanol"

Claim Element	Glaxo's Proposed Construction	Teva's Proposed Construction
"ethanol"	An organic compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07.	A chemical of the nomenclature CH_3CH_2OH, namely ethanol.

a. Ethanol Is An Organic Compound Composed Of A Lower Aliphatic Hydrocarbon Having Two Carbon Atoms And One -OH Group

Defendant's proposed construction acknowledges the chemical formula of ethanol containing two carbon atoms and one -OH group. The only real dispute that defendant seems to have with Glaxo's proposed construction of "ethanol" is Glaxo's inclusion of the phrase "An organic compound comprising a lower aliphatic hydrocarbon group." Every undergraduate

chemistry student is taught organic chemistry and the basic structure of organic alcohols – aliphatic hydrocarbons containing at least one -OH (hydroxyl) group. (Anderson Opening Rpt.[3] ¶ 77 and Ex. 9; Ethanol is one of the most basic of organic alcohols, so much so that REDACTED

Even Webster's New Collegiate Dictionary (1973), relied upon by defendant, defines ethanol as "ALCOHOL," which, in turn, is defined as: "2. any of various compounds that are analogous to ethyl alcohol in constitution and that are *hydroxyl derivatives of hydrocarbons*." (Teva Claim Construction Appendix Ex. C) (emphasis added) (D.I. 102). Glaxo's construction is a specific description of the basic chemical structure of "ethanol" that is necessary and sufficient to define the plain and ordinary meaning of ethanol as understood by one of ordinary skill in the art.

Ethanol has the following chemical structure:

$$CH_3 — CH_2 — OH$$

(*See* CRC Handbook of Chemistry and Physics, C-296 (59th ed. 1978), Anderson Opening Rpt. ¶ 72 and Ex. 8). The chemical structure of ethanol may be viewed as composed of[5] two parts. (*See* Morrison, R. and Boyd, R., Organic Chemistry, 200 (4th ed. 1983), Anderson Opening Rpt. ¶ 77 and Ex. 9). The first part is a straight chain aliphatic hydrocarbon that contains two carbon

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[3] "Anderson Opening Rpt." refers to "Bradley D. Anderson, Ph.D., Fed. R. Civ. P. 26(a)(2) Expert Witness Report Concerning The Issue of Infringement of Glaxo's '249 Patent" attached as Exhibit A to the Anderson Declaration submitted on June 30, 2006. (D.I. 98).

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[5] To the extent defendant objects to Glaxo's use of the word "comprising" in Glaxo's proposed construction, the words "composed of" may be substituted for better precision and to avoid the objection.

atoms and associated hydrogen atoms. (Anderson Opening Rpt. ¶¶ 72, 77 and Ex. 9). Ethanol is considered a lower aliphatic hydrocarbon because it contains two carbon atoms, which is characteristic of shorter chain hydrocarbons (*i.e.*, those within the range of about one to four carbon atoms). (*Id.* at ¶ 77). The second part of ethanol is one -OH (hydroxyl) group. (*Id.* at ¶¶ 72, 75, 77 and Ex. 9). An -OH (hydroxyl) group is a functional group that occurs on at least one carbon atom and characterizes the properties of an organic alcohol. (*See* Morrison, R. and Boyd, R., Organic Chemistry, 200 (4th ed. 1983), Anderson Opening Rpt. ¶ 77 and Ex. 9).

Glaxo's construction uses only those words necessary to describe the chemical structure of ethanol: "An organic compound ~~comprising~~ composed of a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07." There are no extraneous limitations or descriptions of unnecessary elements. Glaxo's construction is the plain and ordinary meaning of the word ethanol as understood by one of ordinary skill in the art of pharmaceutical formulation and development. (Anderson Opening Rpt. ¶¶ 72, 77 and Exs. 8 and 9; Anderson Rebuttal Rpt.[6] ¶ 13).

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b. Defendant's Construction Does Not Explain The Structure Of Ethanol

Defendant's proposed construction of ethanol lacks description of what ethanol means to one of ordinary skill in the art. Defendant's construction is incomplete and redundant, simply

[6] "Anderson Rebuttal Rpt." refers to "Bradley D. Anderson, Ph.D., Fed. R. Civ. P. 26(a)(2) Rebuttal Expert Witness Report" attached as Exhibit B to the Anderson Declaration submitted on June 30, 2006. (D.I. 98).

reciting the chemical formula and construing ethanol as "namely ethanol." This is not an appropriate construction of the claim language. The purpose of claim construction is to provide meaning and to " 'elaborate the normally terse claim language in order to understand and explain, but not to change, the scope of the claims.' " *Embrex*, 216 F.3d at 1347 (quoting *Scripps Clinic*, 927 F.2d at 1580). Defendant's construction does not explain the structure of ethanol, and, consequently, does not properly construe the claim element. Glaxo's construction of ethanol explains the structure of ethanol and, as a result, accomplishes the purpose of claim construction.

The '249 patent specification and prosecution history repeatedly disclose and teach the use of ethanol to stabilize an aqueous formulation of ranitidine for oral administration, without expressly defining ethanol. A patent specification, however, need not define what is understood by those of ordinary skill in the art. *See Koito Mfg. Co., Ltd. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) ("This Court has repeatedly explained that a patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art."). Ethanol is commonly understood by those of ordinary skill in the art as an organic alcohol composed of a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07. (Anderson Opening Rpt. ¶¶ 72, 75, 77 and Exs. 8 and 9; **REDACTED**

REDACTED The word "ethanol" alone is sufficient to convey this basic meaning to anyone of ordinary skill in the art, and defendant's suggestion to the contrary is contradicted by the evidence. (*See* Teva Opening Br.[7] p. 4).

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[7] "Teva Opening Br." refers to "Teva's Opening Brief in Support of its Claim Constructions" submitted on June 30, 2006. (D.I. 101).

Glaxo is not construing ethanol in any "unique or special manner," nor does Glaxo need to "bootstrap its infringement argument into the definition of 'ethanol'." (Teva Opening Br. pp. 8-9). There is only one ethanol[8], and defendant has engaged in a classic equivalent substitution of another lower aliphatic alcohol, propylene glycol, to gain the benefit of the claimed invention by making an insubstantial change from the patented invention with the formulation of its accused product. Glaxo's construction describes the chemical structure of ethanol using a textbook description that is necessary and sufficient to define the plain and ordinary meaning of ethanol as understood by those of ordinary skill in the art of pharmaceutical formulation and development. Glaxo respectfully requests that the Court adopt Glaxo's proposed construction for the claim element "ethanol."

2. Claims 1-12: "a stabilizing effective amount of"

Claim Element	Glaxo's Proposed Construction	Teva's Proposed Construction
"a stabilizing effective amount of"	An amount sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.	An amount of a stabilizer that is sufficient to cause a statistically significant increase in the time it takes for an aqueous formulation containing ranitidine hydrochloride to lose 5 percent of the ranitidine present (the "T95" value) as compared to the same formulation without the stabilizer.

Glaxo's proposed construction of "a stabilizing effective amount of" is directly supported by the language of the claims, the specification and the prosecution history of the '249 patent,

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[8] Glaxo's construction follows the rules of claim construction and does not "bring[] just about every other alcohol and non-alcohol compound with at least two carbon atoms and one -OH group within the scope of the claims." (Teva Opening Br. pp. 9-10).

and by Federal Circuit law as described in Glaxo's Opening Claim Construction Brief.[9] This functional claim language describes the amount of ethanol required to stabilize ranitidine effectively in an aqueous formulation for oral administration. REDACTED

REDACTED In other words, "a stabilizing effective amount of" is the amount of stabilizer sufficient to enhance the stability of the ranitidine active ingredient in an aqueous formulation for oral administration.

Defendant's proposed construction of "a stabilizing effective amount of" does not describe what the claimed function is. Rather, it improperly reads illustrative test measurement details into the patent claim language. Defendant relies on a declaration submitted during the prosecution of the '249 patent that provided stability test data and analysis as support for the claimed function of ethanol – to enhance the stability of ranitidine – in an aqueous formulation of ranitidine for oral administration. The data and analysis submitted to the Patent and Trademark Office ("PTO") in the declaration are evidence that the claimed function occurs using the amounts of ethanol claimed. Such evidence does not, however, constitute the definition of the claimed function itself. Defendant ignores the reason the declaration was submitted and proposes a construction that improperly reads extraneous limitations into the patent claims. *See Bayer*, 279 F.3d at 1348 ("While a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history.").

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[9] Glaxo respectfully refers the Court to its Opening Claim Construction Brief at pp. 23-28 for a detailed discussion and citation of the intrinsic evidence supporting Glaxo's proposed claim construction. (D.I. 97).

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a. The '249 Specification Supports Glaxo's Claim Construction

The specification of the '249 patent explains that "the *stability of ranitidine* in aqueous based formulations and more particularly aqueous based formulations for oral administration *may be substantially enhanced* by the addition of ethanol to the formulation." ('249 Patent Col. 1:40-44, Langer Decl., Ex. 1) (emphasis added). The specification goes on to explain that "[t]he *amount* of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*." (*Id.* at Col. 1:54-56) (emphasis added). From these descriptions in the specification, it is clear that "a stabilizing effective amount of" is the amount sufficient to enhance the stability of the ranitidine active ingredient in an aqueous formulation for oral administration. (*See* '249 File History at G000267-68, G000140, Langer Decl., Ex. 10).

The specification does not specify or require that enhanced ranitidine stability be measured and assessed using the detailed measurement criteria in defendant's proposed construction. An inventor does not have to describe in the specification how to determine a claimed functional limitation – such as "a stabilizing effective amount of" – where a person of ordinary skill in the art could readily determine the amount claimed without undue experimentation. *See* 35 U.S.C. § 112; *see Kao Corp. v. Unilever United States, Inc.*, 334 F. Supp. 2d 527, 549-552 (D. Del. 2004). In particular, "[t]he Federal Circuit has stated that the phrase ' 'effective amount' is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation.' " *Kao Corp.*, 334 F. Supp. 2d at 552 (quoting *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003)); *see also In re Spiller*, 500 F.2d 1170, 1180 (C.C.P.A. 1974) ("There is nothing indefinite in the use of claim language which defines particular amounts according to a functional criterion."); *In re Conley*, 490 F.2d 972, 975-76 (C.C.P.A. 1974). The limitation "a

stabilizing effective amount of" as used in the '249 patent can be readily determined without undue experimentation, as demonstrated by Professor Anderson's analysis and testimony, and by the Declaration by Dr. John Hempenstall submitted to the PTO during prosecution of the '249 patent ("Hempenstall Declaration").

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'249 File History at G000204-211, Langer Decl., Ex. 10). One of ordinary skill in the art would understand from reading the '249 patent that the enhanced stability of ranitidine in an aqueous formulation for oral administration could be readily assessed by comparing it to the stability of Glaxo's earlier aqueous formulation of ranitidine for oral administration, as disclosed in Example 3 of the cited prior art Padfield '820 patent, which did not contain ethanol (or an equivalent stabilizer).[11] (Anderson Opening Rpt. ¶ 35; Anderson Rebuttal Rpt. ¶¶ 26-27). The detailed test measurements supporting the enhanced stability determination cannot be incorporated as limitations into the '249 patent claim as suggested by defendant.

b. The Hempenstall Declaration Supports Glaxo's Claim Construction

The Hempenstall Declaration "provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 [Padfield '820 patent] in terms of the *stability of the ranitidine* in the composition." ('249 File History at G000205, Langer Decl., Ex. 10) (emphasis added). Dr. Hempenstall stated that: "In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and *surprising enhancement in the stability of ranitidine* is achieved by the addition of ethanol to the

[11] "Padfield '820 patent" refers to British Patent Application No. GB 2142820A identified and described in the '249 patent at Col. 1:23-38. ('249 File History at G000191-95, Langer Decl., Ex. 10).

formulation." (*Id.* at G000209, ¶ 5) (emphasis added). Dr. Hempenstall concluded that "ethanol has a *beneficial effect* upon the *stability of ranitidine* in aqueous based formulations . . . ." (*Id.* at G000211, ¶ 7) (emphasis added). The Hempenstall Declaration supports Glaxo's claim construction.

Defendant's proposed construction, on the other hand, improperly reads into the claims extraneous detailed measurement criteria from the Hempenstall Declaration. As a matter of law, these extraneous limitations from the prosecution history of the '249 patent must not be included in the construction of the claim language "a stabilizing effective amount of." *See Bayer*, 279 F.3d at 1348 ("While a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history.").

Dr. Hempenstall's explanations support the plain and ordinary meaning of the disputed claim language and illustrate what one of ordinary skill in the art would understand from reading the claims, the specification, and the prosecution history of the '249 patent. The amount of ethanol required in the formulation is an amount sufficient to enhance the stability of ranitidine in the aqueous formulation for oral administration. This is consistent with Glaxo's proposed construction.

c. There Is No Legal Or Evidentiary Basis For Defendant's Proposed Limitation Requiring A Comparison Of t_{95} Stability Data For The "Same Formulation" With And Without The Stabilizer At Issue

Defendant hopes to use its strained proposed construction as a springboard for its non-infringement argument. Defendant's construction improperly limits the disputed claim element by requiring a comparison of a formulation with stabilizer to "the *same* formulation without the stabilizer." (Teva Opening Br. p. 11) (emphasis added). The '249 patent specification and

prosecution history do not require such a limitation. By its proposed construction, defendant argues that Glaxo can only prove infringement by comparing stability data for defendant's accused ANDA Product formulation both with and without propylene glycol. There is no legal or evidentiary support for defendant's claim construction.

Defendant's proposed construction is based on a misreading of the '249 patent prosecution history. In the prosecution history, Dr. Hempenstall stated: "The advantageous effect resulting from the addition of ethanol to an aqueous based ranitidine formulation *can readily be* determined by comparing the stability of the ranitidine in a formulation according to the present invention and the same formulation but without the added ethanol." ('249 File History at G000209 ¶ 5, Langer Decl., Ex. 10) (emphasis added). Dr. Hempenstall did not say "*must be* determined only in this way," because one of ordinary skill in the art would understand that the enhanced stability of ranitidine in an aqueous formulation for oral administration can also be assessed by other means.

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This is the same comparison used by Glaxo in the *Pharmadyne* case and relied on by that court to find patent infringement by Pharmadyne's ANDA product. *Glaxo Wellcome, Inc. v. Pharmadyne Corp.*, 32 F. Supp. 2d 265, 285-87 (D. Md. 1998).

One of ordinary skill in the art would understand that the '249 patent does not require the use of only a certain, specific type of comparative stability data in order to determine whether a

product uses "a stabilizing effective amount of" a stabilizer.

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It is also clear from the Hempenstall Declaration that the formulations being compared were not precisely "the same," nor do they need to be, as defendant proposes in its claim construction. (Teva Opening Br. pp. 11-14). The applicant explained in its May 10, 1991 Request for Reconsideration sent to the PTO that the Hempenstall Declaration:

> provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 [the '820 patent] in terms of the stability of the ranitidine in the composition. In this connection, it is noted that the liquid formulation without ethanol which is used in the Declaration for purposes of comparison is the *same as the formulation of Example 3 of Padfield et al. ['820 patent]*. Accordingly, the Declaration presents a direct *comparison between* a composition according to the *present invention* and a composition according to the *prior art*.

('249 File History at G000205, Langer Decl., Ex. 10) (emphasis added). Example 3 of the prior art Padfield '820 patent, copied in Paragraph 6 of the Hempenstall Declaration as the formulation "Without Ethanol," provides:

	With Ethanol % w/v	Without Ethanol % w/v
Ranitidine Hydrochloride	1.68	1.68
Ethanol	7.5	
Potassium dihydrogen orthophosphate	0095 [sic]	0.095
Disodium hydrogen orthophosphate anhydrous	0.350	0.350
Hydroxypropylmethylcellulose	*qs*	*qs*
Preservative	*qs*	*qs*
Sweetening agents	*qs*	*qs*
Flavour	*qs*	*qs*
Purified water BP to	100ml	100ml

(*Id.* at G000210, ¶ 6) (emphasis added). The formulation description in the Hempenstall Declaration specifically allows that at least the "Hydroxypropylmethylcellulose," "Preservative," "Sweetening agents" and "Flavour" may all be different in kind and/or amount[12], even though Dr. Hempenstall refers to the formulations as "the same."

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Defendant's proposed construction improperly reads into the claims extraneous limitations that are not supported by the specification or prosecution history. By requiring comparison of a formulation with stabilizer to "the *same* formulation without the stabilizer,"

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[12] The "qs" notation allows for variable amounts as are sufficient (*quantum sufficit*), of which the Court may take judicial notice. *See* Fed. R. Evid. 201; *Ieradi v. Mylan Labs., Inc.*, 230 F.3d 594, 600 n.3 (3d Cir. 2000) ("Under Federal Rules of Evidence 201, we may take judicial notice at any stage of the proceeding of a fact not subject to reasonable dispute that is capable of (continued).

defendant attempts to avoid a finding of patent infringement without any legal citation or evidentiary basis to support defendant's proposed construction. Glaxo urges the Court to reject defendant's unduly restrictive and improper claim construction.

d. Detailed Statistical Measurements Of Stability Are Evidence Of Infringement – They Are Not Claim Limitations

Defendant's construction is further improper as a result of its attempt to construe detailed statistical measurement criteria for assessing stability as claim limitations. Defendant's characterization of the measurement criteria and its reliance on the Hempenstall Declaration as a basis for including this measurement criteria as a claim limitation is misplaced. The t_{95} value is a statistical measure of the stability of an active ingredient in a pharmaceutical formulation. (Anderson Opening Rpt. at ¶¶ 44-47). This statistical measure is a way to assess whether stability is enhanced, and it is evidence of infringement.[13] (*Id.*) The method of proof of the claimed function (and of infringement), however, is not a claim limitation. Applicant never made such an argument in the prosecution history, and defendant does not cite any law or evidence to support such a far-fetched proposition.

Glaxo respectfully requests that the Court adopt Glaxo's proposed claim construction for the claim language "a stabilizing effective amount of" to mean an amount sufficient to enhance

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accurate and ready determination by resort to a source whose accuracy cannot be reasonably questioned."); *see, e.g.*, Random House Webster's Unabridged Dictionary, 1577 (2d ed. 1998).

[13] One of ordinary skill in the art would know that enhanced ranitidine stability may be determined by statistical means. (Anderson Opening Rpt. ¶¶ 20-22, 41-49). The t_{95} value is the time (t) required for the amount of ranitidine in the aqueous formulation at room temperature to degrade to 95% of its initial concentration at the time of formulation. (*Id.*). The FDA requires an applicant to perform stability testing of its proposed drug product, and the FDA provides standard industry guidance that calculations of shelf-life from stability study data be based on the lower 95% confidence limit of the t_{95} value rather than the t_{95} value itself. (*See* 21 C.F.R. § 211.166, Langer Decl., Ex. 20; FDA Guidance at G0035954-959, Langer Decl., Ex. 18; (continued).

the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.

3. Claim 2: "2.5% to 10% weight/volume ethanol" And Claims 3 And 11: "7% to 8% weight/volume ethanol"

Claim Element	Glaxo's Proposed Construction	Teva's Proposed Construction
"2.5% to 10% weight/volume ethanol"	2.5% to 10% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.	2.5% to 10% weight/volume ethanol.
"7% to 8% weight/volume ethanol"	7% to 8% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.	7% to 8% weight/volume ethanol.

In contrast to defendant's proposed construction, Glaxo's proposed construction for "2.5% to 10% weight/volume ethanol" and "7% to 8% weight/volume ethanol" is supported by the claims, the specification and the prosecution history of the '249 patent, and by Federal Circuit law. In particular, defendant ignores the '249 patent specification where it explains that:

> [T]he amount of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range *2.5% to 10%*, and more particularly is between 5 to 10% w/v, *more especially 7-8% w/v*.

('249 Patent Col. 1:54-56, Langer Decl., Ex. 1) (emphasis added). This portion of the '249 patent specification makes clear the connection between ethanol's function of enhancing ranitidine stability and the amount of ethanol required to accomplish that function. They are

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Anderson Opening Rpt. ¶ 22). Defendant's proposed construction does not properly refer to or (continued).

integrated concepts as claimed in the '249 patent, not independent elements as argued by defendant.

During prosecution, all of the pending claims, including issued claims 2, 3, and 11, were rejected on the ground that the applicant had not demonstrated that the invention produced any unexpected results. The Examiners stated:

> Padfield et al. ['820 patent] teach the *enhanced stability of aqueous compositions of ranitidine* formulated at a pH in the range of 6.5 to 7.5. The applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the rage [sic, range] of 6.5 to 7.5 and with the addition of ethanol. *It has not been demonstrated in the record, by means of experimental data, that the applicant's invention produces any unexpected results.* The disclosure, as presented, is insufficient to overcome the prior art without the aid of experimental data to show a definite improvement over the GB [Padfield '820] patent. Since the GB [Padfield '820] patent teaches an aqueous composition of ranitidine, it is considered well within the state of the art to choose ethanol as an additive which would be considered pharmaceutically acceptable when formulating this composition. Absent evidence to the contrary, the addition of ethanol is considered merely to be a choice among known conventional excipients.

('249 File History at G000200, Langer Decl., Ex. 10) (emphasis added). In response, Glaxo filed a Request for Reconsideration and enclosed the Hempenstall Declaration. (*Id.* at G000204-211).

In his Declaration, Dr. Hempenstall disclosed the results of stability testing using 2.5% to 10% ethanol in aqueous formulations of ranitidine for oral administration, which demonstrated the "beneficial effect" of ethanol on the stability of ranitidine in aqueous based formulations. (*Id.* at G000211 ¶¶ 6-7). Dr. Hempenstall explained: "In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and surprising *enhancement in the stability* of ranitidine is achieved by the addition of ethanol to the formulation." (*Id.* at G000209, ¶ 5)

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even discuss the lower 95% confidence limit of the t_{95} value as set forth in the FDA guidance.

(emphasis added). In response to the Request for Reconsideration and the Hempenstall Declaration, which demonstrated the claimed function of ethanol – enhanced ranitidine stability – the PTO issued a Notice of Allowability of all of the claims. (*Id.* at G000212). This claimed function of ethanol – enhanced ranitidine stability – was critical to the allowance of all of the '249 patent claims and is now part of those claims, including claims 2, 3, and 11. *See Impax Labs.*, 356 F.3d at 1356 ("[S]ubject matter surrendered via claim amendments during prosecution is also relinquished for other claims containing the same limitation. This court follows this rule to ensure consistent interpretation of the same claim terms in the same patent.") (citing *Builders Concrete*, 757 F.2d at 260). Glaxo's proposed construction for the disputed claim language recognizes this claimed function of ethanol to enhance ranitidine stability.

Glaxo's proposed construction also recognizes the dependency of claims 2 and 3 on claim 1 while defendant's construction ignores claim dependency. It is basic patent law that dependent claims incorporate all of the limitations of the independent claim from which they depend. *See* 35 U.S.C. § 112 ¶ 4; *In re Beaver*, 893 F.2d 329, 330 (Fed. Cir. 1989). In dependent claims 2 and 3, the claim language "2.5% to 10% weight/volume ethanol" and "7% to 8% weight/volume ethanol" further limits the functional amount of ethanol in claim 1 as a numeric range having a stabilizing effect on ranitidine in an aqueous formulation for oral administration. Contrary to defendant's assertions, Glaxo's construction is consistent with the '249 patent specification and prosecution history because Glaxo emphasized during prosecution ethanol's distinguishing function of enhancing the stability of ranitidine in an aqueous formulation for oral administration when added to that formulation.

Glaxo respectfully requests that the Court adopt Glaxo's proposed construction for the claim language "2.5% to 10% weight/volume ethanol" and "7% to 8% weight/volume ethanol."

4. Claims 1-10: "aqueous formulation for oral administration," And Claims 11-12: "aqueous formulation of ranitidine suitable for oral administration"

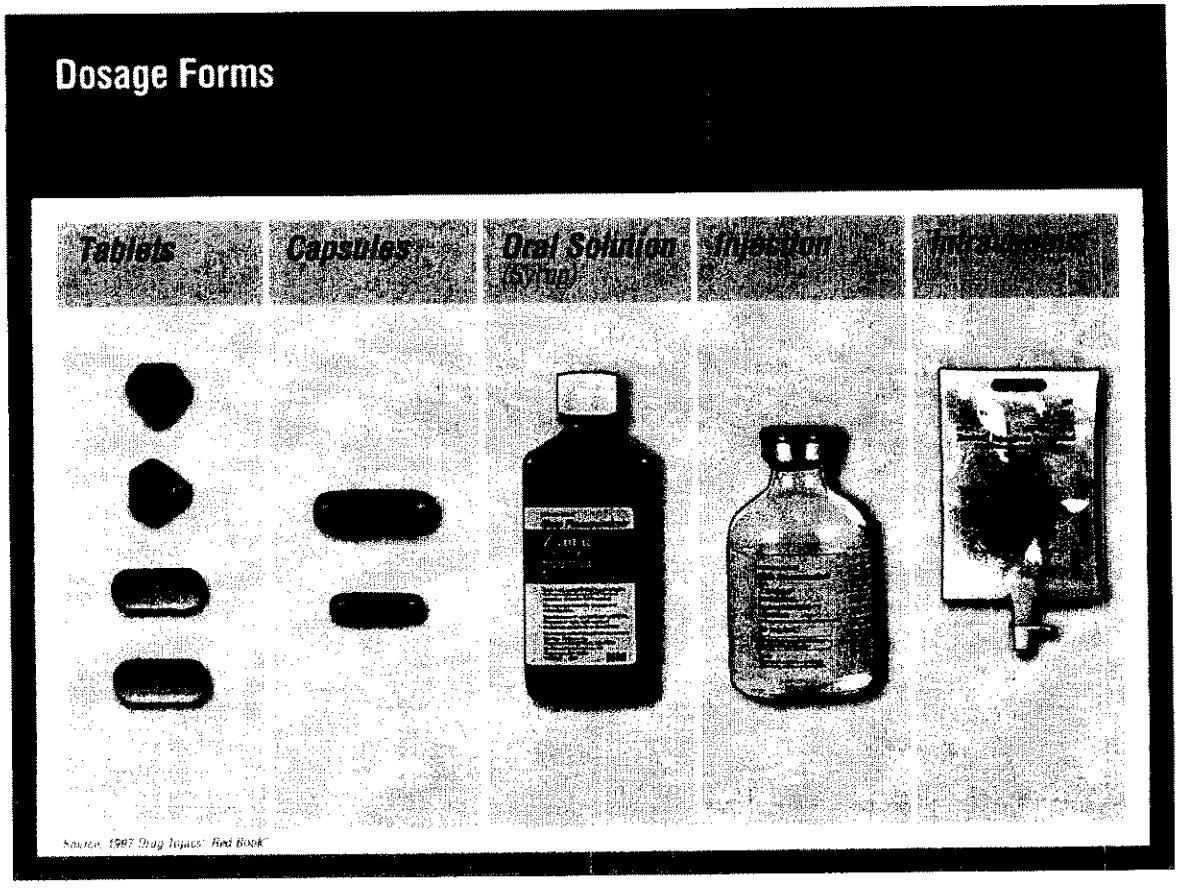
Claim Element	Glaxo's Proposed Construction	Teva's Proposed Construction
"aqueous formulation for oral administration"	A water based formulation, wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption.	This clause need not and should not be construed, given Teva's judicial admission, as stated during the June 30, 2005 telephone conference with the Court.
"aqueous formulation of ranitidine suitable for oral administration"	A water based formulation of ranitidine, wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption.	This clause need not and should not be construed, given Teva's judicial admission, as stated during the June 30, 2005 telephone conference with the Court.

Defendant does not dispute Glaxo's proposed construction of "aqueous formulation for oral administration" and "aqueous formulation of ranitidine suitable for oral administration." Defendant asserts that these claim elements should not be construed because it has stipulated that its accused ANDA Product satisfies these claim elements. (Teva Opening Br. pp. 18-19). Even though defendant has made such a stipulation, Glaxo respectfully requests that the Court adopt Glaxo's proposed construction because these claim limitations provide the framework necessary to construe all of the disputed limitations within the proper context of the claim as a whole. *See Griffin*, 285 F.3d at 1033; *Pitney Bowes*, 182 F.3d at 1305.

Defendant suggests that because these claim elements are part of the preamble of claims 1-12 they would generally not serve as a limitation of the patent claims. (Teva Opening Br. at p. 19 n.8). Glaxo disagrees. The claim elements "aqueous formulation for oral administration" and "aqueous formulation of ranitidine suitable for oral administration" clearly give life and meaning to the other elements of the claims and provide guidance in understanding and

construing the claims. Thus, they do serve as limitations of the claims. *See Griffin*, 285 F.3d at 1033; *Pitney Bowes*, 182 F.3d at 1305 ("If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim.") (quoting *Kropa v. Robie*, 187 F.2d 150, 152 (C.C.P.A. 1951)).

As illustrated in the graphic below, there are a variety of solid drug dosage forms, such as tablets, and capsules, and aqueous drug dosage forms, such as oral solutions (*e.g.*, syrups), injections and intravenous solutions:



At issue in this case are only aqueous formulations of ranitidine (or one of ranitidine's physiologically acceptable salts) suitable for oral administration, *i.e.*, oral solution (syrup)

formulations. To distinguish the claimed invention from other drug dosage forms, the specification of the '249 patent explains:

> We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly *aqueous based formulations for oral administration* may be substantially enhanced by the addition of ethanol to the formulation.

('249 Patent Col. 1:40-44, Langer Decl., Ex. 1) (emphasis added). Similarly, both independent claims, 1 and 11, of the '249 patent provide:

> 1. A pharmaceutical composition which is an *aqueous formulation for oral administration* of an effective amount of ranitidine and/or one or more physiological acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.
>
> 11. A pharmaceutical composition which is an *aqueous formulation of ranitidine suitable for oral administration* containing 150 mg ranitidine per 10 ml dose expressed as a free base, said formulation having a pH in the range of 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

(*Id.* at Col. 2:67 - Col. 3:4 and Col. 4:11-16) (emphasis added). The claim limitations "aqueous formulation for oral administration" and "aqueous formulation of ranitidine suitable for oral administration" limit the scope of the claims to aqueous dosage forms for oral administration and, therefore, provide life and meaning to the claims of the '249 patent. The construction of these limitations is also necessary to construe other disputed claim elements properly and within the context of the patent and the claims as a whole. These limitations should, therefore, be construed by the Court. *See Griffin*, 285 F.3d at 1033; *Pitney Bowes*, 182 F.3d at 1305. Glaxo respectfully requests that the Court adopt Glaxo's proposed constructions for the claim language "aqueous formulation for oral administration" and "aqueous formulation of ranitidine suitable for oral administration."

V. CONCLUSION

Glaxo's proposed construction of the disputed and undisputed claim limitations in the '249 patent is consistent with the intrinsic evidence of record and with the plain and ordinary meaning of the words as understood by a person of ordinary skill in the art. Glaxo respectfully requests that the Court adopt Glaxo's proposed construction of the disputed and undisputed claim limitations in the '249 patent.

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CERTIFICATE OF SERVICE

I hereby certify that on August 4, 2006, I filed a redacted version of **PLAINTIFF GLAXO'S ANSWERING BRIEF TO DEFENDANT TEVA'S OPENING BRIEF IN SUPPORT OF ITS CLAIM CONSTRUCTION** with the Clerk of Court and will hand deliver such filing to the following:

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